Long-Term Analysis in Acute Coronary Syndrome: are there any Differences in Morbidity and Mortality?

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Abstract

Background: Heart failure (HF) is extremely important as a predictor of morbidity and mortality in patients with acute coronary syndrome (ACS).

Objective: To evaluate the predictors of morbidity and mortality in ACS in the long term.

Methods: A cohort study of 403 consecutive patients with complaints of chest pain. Demographic, clinical, laboratory and therapy-related data were described and the patients were evaluated during hospitalization and for up to eight years after being discharged, for the presence or absence or cardiovascular events and deaths.

Results: There were 403 patients complaining of chest pain, 65.8% of whom had been diagnosed as having ACS without ST elevation, 27.8% had ACS with ST elevation and 6.5% without ACS. Among such patients, the 377 patients with ACS were evaluated (37.9% of whom were females), and the mean age was 62.2 ± 11.6 years. The presence of HF before or during hospitalization influenced mortality. Among the prognostic factors, emphasis should be placed on the initial creatinine level, with the cutoff point being set at 1.4 mg/dl (accuracy = 62.1%, HR = 3.27; p < 0.001). We noted a worse prognosis for each additional ten years of age (HR = 1.37, p < 0.001) and for each increment of 10bpm heart rate (HR = 1.22 p < 0.001). As for the therapies used before and after 2002, there was an increase of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), statins and antiplatelet agents, having an impact on mortality.

Conclusion: HF upon admission, creatinine, age and HR were independent predictors of mortality. It was observed that HF patients treated before 2002 had a worse survival when compared with that seen after 2002 and the change in therapy was responsible for it. (Arq Bras Cardiol 2010;95(6):705-712)

Keywords: Acute coronary syndrome/mortality/trends; heart failure; morbidity; drug evaluation.

Introduction

Acute coronary syndrome (ACS) is an ancient and frequent disease, with consequences in society not only in economic terms, but also in rates of mortality. In the United States of America (USA), cardiovascular disease showed a prevalence of 71.3 million; coronary artery disease, 13.2 million; and congestive heart failure, 5 million. Overall mortality from cardiovascular disease in 2001 was 6 billion and 148 million, representing 12.5%; for 2020, there is a forecast of 32% of deaths from cardiovascular disease (CVD) for a population estimated at 7.8 billion; and for 2030 the forecast is 33% of CVD deaths for a population of 8.2 billion.

In Brazil, in 2005, total deaths from ischemic heart disease, according to Datasus, was 84,945. São Paulo and Rio de Janeiro were the states with the highest levels. Regardless of socioeconomic class and region of Brazil, circulatory disease represents the largest number of deaths in our population.

In developed countries, coronary heart disease is a major cause of heart failure and morbidity and mortality. The prognosis of heart failure due to acute myocardial infarction (AMI) depends on the extent and severity of ventricular dysfunction, second only to age. Clinical evidence of heart failure usually represents loss of 20% to 25% of left ventricular contraction, with cardiogenic shock if the loss exceeds 40% of muscle mass.

The objective of this study is to assess the demographic and clinical characteristics of patients with acute coronary syndrome admitted to the University Hospital Pedro Ernesto (HUPE) from August 1999 to 2007. In addition, long-term predictors of morbidity and mortality during follow-up of up to eight years were determined.
Methods

We evaluated a cohort of 403 consecutive and prospective patients admitted to the cardiology public service from August 1999 to December 2007 with an initial diagnosis of acute coronary syndrome. In 377 patients, diagnosis of ACS was confirmed through regular clinical visits and telephone conversations. The study was approved by the ethics committee of the institution according to the Helsinki Declaration, and all patients signed the Informed Consent (IC) to participate in the study.

Demographical data, comorbidities, previous history of coronary disease, reports of coronary angiography, percutaneous coronary intervention or coronary artery bypass surgery were described in this population.

We compared invasive risk stratification versus noninvasive risk stratification, as well as the differences between drug treatment with interventionist treatment to assess progress during hospitalization and within the first eight years after discharge, in relation to cardiovascular events and deaths.

Diagnosis upon admission and discharge were evaluated, as well as the number of deaths and events within eight years.

Patients were evaluated and followed up by periodic clinical visits and telephone conversations until December 2008. Complementary methods were not mandatory, and for this study, only those tests performed by patients at the discretion of the attending physician and availability in the hospital were registered.

Patient selection and follow-up

We considered the following inclusion criteria: patients younger than 18; patients who signed the Informed Consent (IC); patients who were diagnosed with acute coronary syndrome as a presumptive diagnosis; clinical picture associated or not to electrocardiographic changes that justified diagnosis, such as ST elevation or depression or T wave inversion.

We considered the following exclusion criteria: acute coronary syndrome secondary to severe gastrointestinal bleeding, surgery, post-invasive procedure, trauma, or car accident. We also considered the following criteria: patients with end-stage cancer or advanced liver disease; incapacity to participate in or indifference to cooperate with the study; refusal to sign the ICF; other conditions making it difficult to participate in the study.

Statistical analysis

All figures were described as mean and standard deviation or median and interquartile range. Categorical data were expressed by percentage.

We applied the Student t test, Mann-Whitney test, chi-square test and Fisher exact test, as applicable.

To construct the survival model were initially used the Kaplan-Meier and log-rank test. The multivariate model was adjusted using the Cox model. After performing the Cox survival analysis, we diagnosed the model to ensure the assumption of proportional hazards. When necessary, we used the stratified Cox model.

To choose the best cutoff point for numeric variables, aimed at predicting mortality, we used the receiver operating characteristic curve (ROC).

All analyses was performed using the program R version 2.9.1. A significance level of 95% was considered in this study, which corresponds to p = 0.05.

Results

Characteristics of sample population

The sample population of this study is composed of 403 patients complaining of chest pain, being 65.8% diagnosed with ACS without ST elevation, 27.8% ACS with ST elevation ACS and 6.5% without ACS. The demographic and clinical characteristics, and risk factors for CAD are presented in Tables 1 and 2. Tables 3 and 4 present the clinical and laboratory characteristics of the study population according to the presence of HF.

Clinical characteristics and therapies related to mortality

The main clinical characteristics and therapies related to mortality are Killip classification, change in systolic function on echocardiography, presence of left bundle branch block (LBBB), presence of HF prior to admission (or any HF condition appearing during hospitalization) and the therapy used before and during hospitalization.

With regard to Killip classification, classes II and III have similar mortality rates (58.6% vs 55.6%, respectively), class IV has 100% mortality and the class I has 26% mortality (p = 0.00126).

The same was observed concerning the change of left ventricular systolic function on echocardiography, in which normal function was observed in 22.3%, mild dysfunction in 37.5%, moderate in 36.6% and severe in 62.95 % of deaths (p = 0.00017).

Regarding the presence of LBBB, we noted a greater prevalence on deaths (36.8%) compared to survivors (30.3%), although with no statistically significant difference (p = 0.610).

Table 1 - Demographic characteristics of the sample population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Average follow-up period (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n%)</td>
<td>234 / 62.07</td>
</tr>
<tr>
<td>Female (n%)</td>
<td>143 / 37.93</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>62.20 ± 11.60</td>
</tr>
<tr>
<td>Weight (kg) [min – max]</td>
<td>71.16 [41 - 120]</td>
</tr>
<tr>
<td>Height (cm) [min – max]</td>
<td>165 [119 - 198]</td>
</tr>
<tr>
<td>BMI (median) [1st and 3rd quartiles] kg/m²</td>
<td>25.40 [23.40 - 27.90]</td>
</tr>
<tr>
<td>Hypertension (n%)</td>
<td>296 / 78.52</td>
</tr>
<tr>
<td>Smoking (n%)</td>
<td>131 / 34.75</td>
</tr>
<tr>
<td>Dyslipidemia (n%)</td>
<td>169 / 44.83</td>
</tr>
<tr>
<td>Diabetes mellitus (n%)</td>
<td>87 / 23.08</td>
</tr>
</tbody>
</table>

BMI - body mass index.
Concerning the final diagnosis, the proportion of patients who subsequently died was similar irrespective of the form, whether by ACS with ST elevation (29.8%), or by ACS without ST elevation (32.4%) (p = 0.467).

The presence of previous HF influenced mortality (with HF = 45.2% vs 28% without HF; p = 0.0004), as well as the presence of HF during hospitalization (HF = 65% vs 24.1% without HF; p = 0.00000021).

Table 5 presents the survival and mortality depending on the therapy used upon admission and after follow-up.

During hospitalization, the patients using thrombolytics had lower mortality, and about the use of diuretics and inotropic agents, there was higher mortality.

In the period of follow up, patients who used beta-blockers and ACE inhibitors had lower mortality. Unlike what was observed in hospital in relation to the use of diuretics, patients who continued use after hospital discharge presented a lower number of deaths. The use of antiplatelet agents has led to lower mortality.

As to interventional therapy, there are more deaths in patients undergoing coronary artery bypass surgery (12.10% of deaths. The use of antiplatelet agents has led to lower mortality.

Comparing the periods before and after 2002, there has been a reduction in mortality with statistically significant difference (19.35% vs 6.32%, p < 0.001), but readmissions had no differences for the periods, without statistical significance (before 2002 = 23.77% vs 27.27% after 2002, p = 0.55).

There were differences on the therapies used according to the period of time and statistical distinction between patients who were treated before and after 2002.

In this cohort, we could observe an increase after 2002 of previous use of betablockers (5.93% to 32.54%; p < 0.001), ACE inhibitors (35.59% to 45.82%; p = 0.071), statins (6.0% to 20.63%; p < 0.001) and diuretics (6.52% to 19.44%; p = 0.003). During hospitalization, there was also increased use of thrombolytics (37.50% to 44.74%; p = 0.46), ASA (73.33% to 86.90%; p = 0.002), clopidogrel (4.20% to 14.29%; p = 0.004). Another relevant aspect was the largest quantity of coronary artery bypass grafts and coronary angioplasties (29.84% to 45.06%; p = 0.005).

Analysis of the sample population according to the time period

The data were analyzed by comparing the population before and after the year 2002. It was noted that 12.10% of patients with ACS had HF before 2002 and 11.16% after 2002. Therefore, the occurrence of HF was similar in both instances.
Table 5 - Mortality and survival according to therapy used upon admission and after clinical follow-up

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Alive n (%)</th>
<th>Deaths n (%)</th>
<th>Total n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytics</td>
<td>38 (73.1)</td>
<td>14 (26.9)</td>
<td>52 (41.9)</td>
<td></td>
</tr>
<tr>
<td>No thrombolytics</td>
<td>49 (68.1)</td>
<td>23 (31.9)</td>
<td>72 (58.1)</td>
<td></td>
</tr>
<tr>
<td>p = 0.6911445</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropic drugs</td>
<td>21 (51.2)</td>
<td>20 (48.8)</td>
<td>41 (11)</td>
<td></td>
</tr>
<tr>
<td>No inotropic drugs</td>
<td>127 (66.5)</td>
<td>64 (33.5)</td>
<td>191 (49.5)</td>
<td></td>
</tr>
<tr>
<td>p = 0.0001272959</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>57 (55.3)</td>
<td>46 (44.7)</td>
<td>103 (27.7)</td>
<td></td>
</tr>
<tr>
<td>No diuretics</td>
<td>205 (76.2)</td>
<td>64 (23.8)</td>
<td>269 (72.3)</td>
<td></td>
</tr>
<tr>
<td>p = 0.000000000000246</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>180 (97.8)</td>
<td>4 (2.2)</td>
<td>184 (45.8)</td>
<td></td>
</tr>
<tr>
<td>No ACEI</td>
<td>98 (45)</td>
<td>120 (55)</td>
<td>218 (54.2)</td>
<td></td>
</tr>
<tr>
<td>p = 0.000000000000216</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>152 (98.8)</td>
<td>2 (1.3)</td>
<td>154 (38.2)</td>
<td></td>
</tr>
<tr>
<td>No beta-blocker</td>
<td>127 (51)</td>
<td>122 (49)</td>
<td>249 (61.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>241 (75.3)</td>
<td>79 (24.7)</td>
<td>320 (85.6)</td>
<td></td>
</tr>
<tr>
<td>No antiplatelet agents</td>
<td>23 (42.6)</td>
<td>31 (57.4)</td>
<td>54 (14.4)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

ACEI - angiotensin-converting enzyme inhibitor.

is interesting to evaluate the interaction between these determinants (Tables 6 and 7).

Although not statistically significant, it is important to note that there was a reversal of opting for surgery. Before 2002, surgery occurred twice more in ACS without ST elevation. After this period, this option did not attract any interest anymore. Although the forms of the disease were not considered, coronary angiography and percutaneous coronary intervention increased significantly after 2002.

Concerning drug therapy, before 2002, only the use of hypoglycaemic was different between diagnoses. Since 2002, only the use of calcium antagonists was different.

However, in the treatment of both diagnoses, from 2002, we should note the increased use of beta-blockers, ACE inhibitors and antiplatelet agents.

Survival analysis

Aiming to evaluate the prognostic impact of HF on admission of patients, there was a univariate analysis of survival using clinical and therapeutic variables. The initial creatinine was strongly related to the prognosis, so we opted to use the ROC curve to select the best cutoff point, which was 1.4 mg/dl, with an accuracy of 62.1%. Of all the treatments tested, only the prior use of diuretics was significant.

In the univariate analysis, the parameters with statistical significance were myocardial infarction (p = 0.015), previous heart failure (p < 0.001), previous arterial hypertension (p = 0.011), admission before 2002 (p = 0.001), creatinine > 1.4 mg/dl (p < 0.001), each increment of ten years of age (p < 0.001) and each increment of 10bpm heart rate (p = 0.001).

Cox survival analysis was used to determine independent predictors of survival, which was stratified through the period of hospitalization (before 2002 or after 2002) to ensure the assumption of proportional hazards.

All univariate variables with p value < 0.05 were included in the model, but only four variables were considered independent predictors: the presence of HF upon admission (HR = 2.73, p < 0.001), initial creatinine > 1.4 mg/dl (HR = 2.33, p = 0.004), extra ten years in age (HR = 1.37, p < 0.001) and extra ten beats in HR (HR = 1.22, p < 0.001).

To better understand the significance of this result, we should refer to Figure 1, which shows the survival of patients with and without HF upon admission, adjusted by the other three variables. Because there are two risk strata, each class is represented by two different curves. It is important to note that patients without HF upon admission progress with the same prognosis, regardless of the year of assistance. However, the presence of HF upon admission is associated with a worse prognosis. The prognosis of patients admitted with heart failure who were treated before 2002 is worse than that of patients from another period.

Discussion

Hospital mortality varies according to the risk group studied, between 1.8% and 23.6%, corresponding respectively to the group of low risk and high risk1, with rates of readmission around 50% in six months, due to worse renal function2. Comparing this study to the literature, we observe that there is not a significant p for readmission, although it has been found in hospital mortality.

From the outcome of these patients, the extent of left ventricular dysfunction after myocardial infarction is the second most important factor of cardiovascular mortality, second only to age3.

There were differences in the behavior of the study population before and after 2002. Although there was no randomization of the study population, we can assume that the difference could be explained by the therapy used and how it was used. The most plausible explanation is that the results showed a better response from 2002, probably due to a more directed treatment set by the Guidelines of the Brazilian Society of Cardiology, which have changed over the years. However, this is only speculation.

Beta-blockers had a good relationship with improvement in symptoms, functional capacity, cardiac remodeling and left ventricular function.2,4 It is known, from studies performed, that the prescription of beta-blockers is a priority in patients with ventricular systolic dysfunction of any cause and any functional class5-13.
In this cohort, there was a statistically significant \( p \) in terms of mortality, comparing the therapies used before and after 2002, when the following drugs have been used previously: diuretics, beta-blockers, ACE inhibitors, statins, aspirin and clopidogrel. This mortality is consistent with the literature, as observed in the studies: SOLVD-treatment\(^6\), MERIT-HF\(^{13}\), CIBIS-II\(^{14}\), US-CARVEDILOL\(^{12}\), COPERNICUS\(^6\), CONSENSUS I\(^{13}\), and V-HEFT-II\(^{16}\) and COMET\(^{10}\).

In this study, there was no statistical difference as to the use of enalapril before and after 2002. The biggest difference was the use of diuretics, beta-blockers, statins, aspirin and antiplatelet agents. The results were statistically significant for the use of clopidogrel, where it was possible to prove similar results.

Heart rate was statistically significant associated with cardiovascular death in a reverse way, i.e., each increment of 10 bpm (HR: 1.22 \( p < 0.001 \)) associated with a worse prognosis of the survival condition. That was confirmed in the study by Rassi et al\(^{17}\), who found that in heart failure with recent onset of symptoms, HR was also statistically significantly associated with each increment of 10 bpm (RR: 1.58 (95%; 1.23 to 2.04))\(^{12}\). This allowed us to analyze the sympathetic activation of HF and suppose, considering that this study is not randomized and that high heart rates are associated with a worse prognosis in cardiovascular disease, although it is examination physical data poorly described in publications. The same was confirmed in the study EPICAL\(^{18}\), in which heart rate was identified by multivariate analysis as an independent predictor of death, both in ischemic heart disease and in dilated cardiomyopathy\(^{17,19}\).

Serum creatinine was also an independent predictor of cardiovascular mortality and very much related with the prognosis (HR: 1.17 for each 1 mg/dl, \( p=0.005 \)), so we chose to use the ROC curve to select the best cutoff point. Thus, we found 1.4 mg/dl, with an accuracy of 62.1% and HR: 3.27 (\( p<0.001 \)), which seems statistically significant in the multivariate model of survival. This finding is consistent with the study reported by Cowie et al\(^{20}\). In this study, the authors determined the prevalence and risk factors that worsened renal function among patients hospitalized for decompensated heart failure and association with subsequent readmissions and mortality. The mechanism of this association is unclear,
but the worsening of renal function is associated with high mortality. It was observed that the worsening of renal function were independently associated with serum creatinine levels upon admission (HR: 3.02, 95% CI, 1.58 to 5.76), pulmonary edema (HR: 0.35 CI 95%, 1.79 to 6.27), history of atrial fibrillation (HR: 0.35 95% CI, 0.18 to 0.67) and therefore a higher cardiovascular mortality.

Just as the study by Cowie et al, several other studies have reported an association between the development of worsening renal function in patients hospitalized with decompensated heart failure and worse clinical outcomes. The mechanism remains unclear, however, according to Rassi et al\textsuperscript{17} serum creatinine was also an independent predictor of mortality, and it is 1.6 times more associated with cardiovascular mortality at each increment of 0.25 mg/dl (HF 95 % 1.33 to 1.92). Rassi et al\textsuperscript{17} also assumed that the persistence at high levels of serum creatinine denote the existence of baseline renal disease, because, after clinical compensation of long-term HF, serum creatinine is expected to reach normal levels\textsuperscript{17}.

In this study, there were differences with respect to HF upon admission: patients with HF upon admission had a worse prognosis than those who did not have HF, which is in line with the literature\textsuperscript{11-21}. With respect to 2002, a difference was also observed: patients who, upon admission, had HF before 2002, showed a worse prognosis than those who were admitted after 2002. As this study was not randomized, and considering that the two guidelines for diagnosis and treatment of HF, of the Brazilian Society of Cardiology of 1999 were revised in 2002, coupled with a more evident invasive treatment after 2002, we may assume that clinical therapy was optimized, showing a statistical difference compared to the better prognosis of survival from 2002. Also in relation to absence of HF upon admission, no difference in prognosis was observed, regardless of the year of assistance, which may evidence the absence of HF as a factor of better prognosis.

It should be noted that the increased use of beta-blockers, antiplatelet drugs, ACE inhibitors and statins were factors responsible for the higher success in treatments since 2002. With respect to beta-blockers, its greater use occurred after 2002, which may be evident by comparing ACSSTE and ACSWSTE before and after 2002 (Table 6).

As for antiplatelet agents, we observed the same result for the periods before and after 2002. For ACEI/ARB, there was also significant evidence in both periods.

Another variable that was considered a predictor of survival by the multivariate model of survival was age, also present in other studies\textsuperscript{19,22-25}. For each additional ten years of age, the prognosis was worse, with HR: 1.37 and p < 0.001.

Creatinine as a predictor of prognosis may be better assessed by the ROC curve, where the best cutoff point was 1.4 mg/dl, with HR: 2.33 with p < 0.004. Just as the study EPICAL and the record OPTIMIZE-HF confirmed the relationship between creatinine and survival, Rassi et al\textsuperscript{17} and Cowie et al\textsuperscript{20} confirmed the same result, where creatinine was considered an important prognostic factor for survival\textsuperscript{17,20,22,25}.

In Figure 1, we can observe that patients without HF upon admission did not differ as to developments, regardless of the year of assistance. However, the presence of HF differs according to the year of assistance: before or after 2002. Both have a worse prognosis, but patients treated after 2002 had a better prognosis compared to those who were seen before. From the consideration of a cohort, this could be
partly attributed to the treatment recommended by the department of Cardiology, which was more strongly focused on the Guidelines of the Brazilian Society of Cardiology, over the years, following its evolution and changes. Since it was not a randomized study, this fact cannot be confirmed.

**Study limitations**

The following limitations are considered in this study:

- medical records filled with incomplete data, missing information.
- lack of cooperation of some patients.
- difficulties inherent in the study, which was partly retrospective.
- initial records of population obtained by different observers.

**Conclusion**

HF patients treated before 2002 had a worse survival than patients treated since 2002.

Even with the difference in survival related to the time period of hospitalization, the impact of clinical and laboratory variables was similar regardless of time of admission.

The presence of HF upon admission, initial creatinine > 1.4 mg/dl, age and HR of patients admitted with ACS are independent predictors of mortality.

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**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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**Study Association**

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